
Mitochondrial DNA mutations in disease and aging.

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Authors: Douglas C Wallace

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Public Summary:

Scientific Abstract:

The human mitochondrial genome involves over 1,000 genes, dispersed across the maternally inherited mitochondrial DNA (mtDNA) and the biparentally inherited nuclear DNA (nDNA). The mtDNA encodes 13 core proteins that determine the efficiency of the mitochondrial energy-generating system, oxidative phosphorylation (OXPHOS), plus the RNA genes for their translation within the mitochondrion. The mtDNA has a very high mutation rate, which results in three classes of clinically relevant mtDNA mutations: recently deleterious germline line mutations resulting in mitochondrial disease; ancient regional variants, a subset of which permitted humans to adapt to differences in their energetic environments; and somatic mutations that accumulate with age eroding mitochondrial energy production and providing the aging clock. Mutations in nDNA-encoded OXPHOS structural genes can also cause mitochondrial disease, and alterations in nDNA mitochondrial biogenesis genes can destabilize the mtDNA and lead to clinical phenotypes. Finally, when combined, nonpathogenic nDNA and mtDNA protein variants can be functionally incompatible and cause disease. The essential functions of the conserved mtDNA proteins and their high mutation rate raise the question as to why the cumulative mtDNA genetic load does not result in species extinction. Studies of mice harboring deleterious mtDNA mutations have shown that the mammalian ovary selectively eliminates the most deleterious mtDNA mutations. However, milder mtDNA mutations are transmitted through the ovary and the female germline and introduced into the general population. This unique genetic system provides a flexible method for generating genetic variation in cellular and organismal energetics that permits species to adapt to alterations in their regional energetic environment.

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